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(71) *Sökande* *Astra AB, Södertälje SE*
Applicant (s)

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Åsa Dahlberg

Åsa Dahlberg

Avgift
Fee

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

NEW USE

Field of the Invention

The invention provides the use of formoterol and budesonide in the treatment of chronic obstructive pulmonary disease (COPD).

Background to the Invention

Chronic obstructive pulmonary disease (COPD) is a term which refers to a large group of lung diseases which can interfere with normal breathing. It is estimated that 11% of the U.S. population has COPD and the incidence is increasing. The two most important conditions covered by COPD are chronic bronchitis and emphysema.

Chronic bronchitis is a long-standing inflammation of the bronchi which causes increased production of mucous and other changes. The patients' symptoms are cough and expectoration of sputum. Chronic bronchitis can lead to more frequent and severe respiratory infections, narrowing and plugging of the bronchi, difficult breathing and disability.

Emphysema is a chronic lung disease which affects the alveoli and/or the ends of the smallest bronchi. The lung loses its elasticity and therefore these areas of the lungs become enlarged. These enlarged areas trap 'stale' air and do not effectively exchange it with fresh air. This results in difficult breathing and may result in insufficient oxygen being delivered to the blood. The predominant symptom in patients with emphysema is shortness of breath.

At present COPD is treated with a variety of inhaled or orally administered bronchodilators, with inhaled anti-cholinergic agents and with orally administered steroids. The problem with these treatments is that none of them are especially effective. Accordingly a new treatment is required.

Description of the Invention

It has surprisingly been found that the combination of formoterol and budesonide is unexpectedly effective in treating COPD.

According to the invention there is provided the use of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

The composition used in the invention optionally additionally comprises one or more pharmaceutically acceptable additives, diluents and/or carriers. The composition is preferably in the form of a dry powder, the particles of which preferably have a mass median diameter of less than 10 μm.

The invention also includes the use of a kit containing:

(i) a vessel containing the first active ingredient;

(ii) a vessel containing the second active ingredient; and

(iii) instructions for the sequential or separate administration of the active ingredients to a patient in need thereof;

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

A patient suffering from COPD can be treated by administering via inhalation a composition as defined above. Alternatively such a patient can be treated by administering via inhalation, sequentially or separately, (i) a dose of the first active ingredient; and (ii) a

dose of the second active ingredient. The doses can be provided to the patient for inhalation in dry powder form.

The invention further provides the use of budesonide and of formoterol in the manufacture of a composition or a kit, as used in the invention, for use in the treatment of chronic obstructive pulmonary disease.

The first and second active ingredients of the kit used in the invention can be administered sequentially or separately to treat respiratory disorders. By sequential is meant that the first and second active ingredients are administered one immediately after the other. They still have the desired effect if they are administered separately but less than about 12 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The molar ratio of the first active ingredient to the second active ingredient in the invention is preferably from 1:2500 to 12:1, more preferably from 1:555 to 2:1, most preferably from 1:133 to 1:6.

Preferably the amount of the first active ingredient used is preferably from 2 to 120 nmol (more preferably from 7 to 70 nmol). The amount of the second active ingredient used is preferably from 0.1 to 5 μmol (preferably 0.15 to 4 μmol) or from 45 to 2200 μg, more preferably from 65 to 1700 μg.

Suitable physiologically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. The first active ingredient is preferably formoterol fumarate, especially the dihydrate.

When the first active ingredient is formoterol fumarate dihydrate, the amount of the first active ingredient used is preferably from 1 to 50 μg, more preferably from 3 to 30 μg.

More preferably the composition or kit used in the invention comprises 6μg of formoterol fumarate dihydrate and 100μg of budesonide, or 4.5μg of formoterol fumarate dihydrate and 80μg of budesonide, either of which is administered up to four times a day. Alternatively the composition or kit of the invention comprises 12μg of formoterol fumarate dihydrate and 200μg of budesonide, or 9μg of formoterol fumarate dihydrate and 160μg of budesonide, either of which is administered once or twice a day.

Most preferably the composition or kit used in the invention comprises 6μg of formoterol fumarate dihydrate and 200μg of budesonide, or 4.5μg of formoterol fumarate dihydrate and 160μg of budesonide, either of which is administered up to four times a day. Alternatively the composition or kit of the invention comprises 12μg of formoterol fumarate dihydrate and 400μg of budesonide, or 9μg of formoterol fumarate dihydrate and 320μg of budesonide, either of which is administered once or twice a day.

Preferably the active ingredient(s) are used in admixture with one or more pharmaceutically acceptable additives, diluents or carriers, preferably in an amount of from 50μg to 25mg per dose, more preferably in an amount of from 50μg to 10mg, most preferably in an amount of from 100 to 2000μg. Examples of suitable diluents or carriers include lactose, dextran, mannitol or glucose. Preferably lactose is used, especially as the monohydrate.

One or more of the ingredients is preferably in the form of a dry powder, more preferably a micronised dry powder, most preferably an agglomerated micronised dry powder. As an alternative to agglomeration, the finely divided active ingredients may be in the form of an ordered mixture with the pharmaceutically acceptable additive, diluent or carrier. An ordered mixture comprises fine particles of an active ingredient in association with coarse

particles of the pharmaceutically acceptable additive, diluent or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those of skill in the art. The particle size of the active ingredients is preferably less than 10μm.

Administration may be by inhalation orally or intranasally. The active ingredients are preferably adapted to be administered, either together or individually, from dry powder inhaler(s), especially the Turbuhaler® (Astra AB), pressurised metered dose inhaler(s), or nebuliser(s).

When the active ingredients are adapted to be administered, either together or individually, from pressurised inhaler(s), they are preferably in micronised form. They are dissolved or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the active ingredients are adapted to be administered, either together or individually, via nebuliser(s) they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The composition or kit used in the invention may optionally be administered as divided doses from 1 to 4, and preferably once or twice a day.

The invention is illustrated by the following Examples which are not intended to limit the scope of the application. In the Examples micronisation is carried out in a conventional

manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler is a trademark of Astra AB.

Example 1

6 Parts by weight of formoterol fumarate dihydrate was mixed with 794 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 2

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 835 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 3

12 Parts by weight of formoterol fumarate dihydrate was mixed with 588 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 400 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 4

6 Parts by weight of formoterol fumarate dihydrate was mixed with 894 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 100 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 5

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 915 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 80 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 6

12 Parts by weight of formoterol fumarate dihydrate was mixed with 788 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 7

6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 8

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

160 Parts by weight of micronised budesonide was mixed with 840 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 9

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

400 Parts by weight of micronised budesonide was mixed with 600 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 10

6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

100 Parts by weight of micronised budesonide was mixed with 900 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 11

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

80 Parts by weight of micronised budesonide was mixed with 920 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Example 12

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

Claims

1. Use of a composition comprising, in admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

2. Use according to claim 1, wherein the composition comprises one or more pharmaceutically acceptable additives, diluents and/or carriers.

3. Use of a kit containing:

(i) a vessel containing a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt;

(ii) a vessel containing a second active ingredient which is budesonide; and

(iii) instructions for the sequential or separate administration of the first and second active ingredients to a patient in need thereof;

in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease.

4. Use according to claim 3, wherein the first and/or second active ingredient is used in admixture with one or more pharmaceutically acceptable additives, diluents and/or carriers.

5. Use according to any one of the preceding claims, wherein the first active ingredient is formoterol fumarate dihydrate.

6. Use according to any one of the preceding claims, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:2500 to 12:1.

7. Use of formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt in the manufacture of a composition as defined in claim 1 or 2 or a kit as defined in claim 3 or 4 for use in the treatment of chronic obstructive pulmonary disease.

8. Use of budesonide in the manufacture of a composition as defined in claim 1 or 2 or a kit as defined in claim 3 or 4 for use in the treatment of chronic obstructive pulmonary disease.

9. A method for the treatment of a patient suffering from chronic obstructive pulmonary disease which method comprises administering to the patient via inhalation, sequentially or separately, a therapeutically effective amount of (i) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt; and (ii) a second active ingredient which is budesonide;

10. A method for the treatment of a patient suffering from chronic obstructive pulmonary disease which method comprises administering to the patient via inhalation a therapeutically effective amount of a composition as defined in claim 1 or 2.

Abstract

The invention provides the use of formoterol and budesonide in the treatment of chronic obstructive pulmonary disease.